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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/680,690	10/06/2000	David B. Weiner	UPN-3906	1044

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/680,690	WEINER ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8,10,12,13,33,34 and 37-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8,10,12,13,33,34 and 37-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed on 1/27/04 has been entered. Claims 11 and 32 have been canceled. Claims 1, 12, 13, 33 have been amended. Claims 1, 3-6, 8, 10, 12, 13, 33, 34, and 37-42 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and new grounds of rejection will not be reiterated. The arguments in 1/27/04 response would be addressed to the extent that they apply to current rejection.

Claim Objections

Claim 42 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 42 recites, "wherein the particle is a viral particle, a complex that comprises two or more protein molecules and a nucleic acid". However, the previous claims (1, 10, 33, 34) exclude a viral particle or protein complex as the particle. Thus, the scope of a dependent claim is broader than the base claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-6, 8, 10, 12, 13, 33, 34, and 37-42 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because of claim recitation, "a cationic amphiphile/DNA complex". It is noted the specification does not specifically define the DNA as it appears in the claim phrase "a cationic amphiphile/DNA complex", thus, given the plain meaning, it encompasses any deoxynucleic acid material including a DNA virus such as adenovirus. However, in the Remarks of 1/27/04, Applicant indicates that this recitation excludes adenovirus. Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "DNA" in claims is used by the claim to mean "DNA excluding adenovirus", while the accepted meaning is "any deoxynucleotide material." The term is indefinite because the specification does not clearly redefine the term. Amending claims to recite a plasmid DNA may obviate this rejection.

The amended claim 12 recites the limitation, "said non-cellular particle". There is insufficient antecedent basis for the limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

ENABLEMENT REQUIREMENT

Claims 1, 3-6, 8, 10, 12, 13, 33, 34, and 37-42 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record and following.

Applicants indicated that claims have been amended to recite "the particles are liposomes and cationic amphiphile/DNA complexes", thus, claims no longer encompass adenoviral vector, and hence the reasonable double presented in *Guibinga* reference should be moot (Remarks, page 7).

The argument has been fully considered but found not persuasive because the amendments place new limitation only on the particle but not the compound. It is noted these claims are drawn to a method of introducing a *compound* into a CD80/CD86-expressing cell, wherein the compound is any nucleic acid including adenoviral vector. Although the new limitation confines the particle to a liposome or a cationic amphiphile/DNA complex, the particle still comprises the compound. The specification defines the compound as encompass any DNA or RNA (page 8, lines 12-14), including recombinant viral expression vectors (e.g. 3rd paragraph, page 40). Accordingly, the claims as written do not exclude the adenoviral vector in the particle. Thus the contrary evidence presented in *Guibinga* reference remains applicable.

Applicants then argue, there is nothing in Deonarian or any other evidence of record support the Office assertion that suboptimal gene delivery indicate a reason to doubt the predictability of the invention (Remarks, page 8, 2nd paragraph).

In response, as discussed in the previous Office actions, *Deonarain* reference clearly illustrated the state of the art around the time of instant effective filing date. When discussing viral vectors available in the art, *Deonarain* teaches, "GENE DELIVERY REMAINS THE MAJOR TECHNOLOGICAL STUMBLING BLOCK IN GENE THERAPY STRATEGIES", (2nd paragraph, page 54), *Deonarain* goes on to review efforts in ligand targeted receptor-mediated DNA complex (as instantly claimed), and concludes, "PRESENTLY, THIS APPROACH IS MUCH LESS EFFICIENT THAN VIRAL GENE DELIVERY" (page 65). "GENE DELIVERY BY LIGAND TARGETED RECEPTOR-MEDIATED ENDOCYTOSIS OF POLYPLEXES *SHOULD* FIND ITS WAY INTO SOME MAIN LINE GENE THERAPY TREATMENT SCHEMES". It is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential for ligand targeting of nucleic acid, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Although the instant specification contemplates this approach, it fails to deliver any nucleic acid via ligand-targeting approach, plasmid or viral vector, specifically to any cell via any route of administration, and it fails to make any fusion protein that comprises even one of the preferred embodiment, i.e. either intracellular portion of the CD28 or intracellular portion of gp41, let alone using such for gene delivery. Accordingly, when considering the state of the art

and the levels of the skilled in the art, given the undeveloped state of gene delivery art, and the unpredictable state of protein and ligand art, coupled with the amount of direction or guidance provided in the specification, the conclusion could only be that the teachings and guidance provided in the specification, as a whole, represent an initial investigation into the feasibility of the development of a useful means for executing gene therapy which awaits further development to the practical level. MPEP states, "WHEN CONSIDERING THE FACTORS RELATING TO A DETERMINATION OF NON-ENABLEMENT, IF ALL THE OTHER FACTORS POINT TOWARD ENABLEMENT, THEN THE ABSENCE OF WORKING EXAMPLES WILL NOT BY ITSELF RENDER THE INVENTION NON-ENABLED." "LACK OF A WORKING EXAMPLE, HOWEVER, IS A FACTOR TO BE CONSIDERED, ESPECIALLY IN A CASE INVOLVING AN UNPREDICTABLE AND UNDEVELOPED ART." (MPEP 2164.02, 03)

With respect to the routes of delivery, Applicants particularly argue that Nakano reference teach using a plasmid vector for gene delivery, which supports rather than doubts the enablement of the claimed invention (Remarks, page 8, 3rd paragraph).

In response, it is noted that claims embrace using any route of delivery of a nucleic acid, and applicants intend to limit the nucleic acid to DNA, such as a plasmid. The Nakano reference is relied on as a showing that not all routes of administration could efficiently deliver a plasmid to obtain a therapeutic effect. *Nakano et al* teach that immune reactivity with plasmid DNA encoding antigenic domains is linked to the injection mode, "DIFFERENT ROUTES OF INJECTION OF HCV E2 PLASMID CAN RESULT IN QUANTITATIVELY AND QUALITATIVELY DIFFERENT HUMORAL IMMUNE RESPONSES". They teach that intraepidermal injection could induce an antibody response that is 100 times higher than the level obtained by intramuscular injection. Even so, they go on to teach the protective

effect of intraepidermal immunization remain to be seen (last paragraph), indicating that a therapeutic effect has not been tested. This teaching when combined with other teachings such as *Torres et al* (J Immunol 1997;158:4529-32, "TRANSFECTED CELLS IN GENE GUN-BOMBARDED SKIN, BUT NOT NEEDLE-INJECTED MUSCLE, PLAY A CENTRAL ROLE IN DNA-INITIATED AB AND CTL RESPONSE" abstract), and *McCluskie et al* (Mol Med 1999 May;5:287-300, "ROUTES OF ADMINISTRATION OF PLASMID DNA VACCINES INFLUENCES THE STRENGTH AND NATURE OF IMMUNE RESPONSES IN MICE AND NON-HUMAN PRIMATES", all directed to the same conclusion, i.e. it is reasonable to raise doubt regarding the enablement of the broadly claimed invention. M.P.E.P. teaches, "IF LITTLE IS KNOWN IN THE PRIOR ART ABOUT THE NATURE OF THE INVENTION AND THE ART IS UNPREDICTABLE, THE SPECIFICATION WOULD NEED MORE DETAIL AS TO HOW TO MAKE AND USE THE INVENTION IN ORDER TO BE ENABLING. THE "PREDICTABILITY OR LACK THEREOF" IN THE ART REFERS TO THE ABILITY OF ONE SKILLED IN THE ART TO EXTRAPOLATE THE DISCLOSED OR KNOWN RESULTS TO THE CLAIMED INVENTION. (MPEP 2164.02, 03) In the instant case, since the skilled artisan has shown that certain route of administration would obtain less or little desirable effect, a doubt is reasonable with respect to whether a therapeutic effect could be achieved via such route of delivery.

Therefore, for reasons of record and those set forth above, the instant specification fails to meet the statutory enablement requirement set forth under 35 U.S.C. §112, 1st paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The prior rejection of claims 1, 10, 11, and 13 under 35 U.S.C. 102(e) as being anticipated by *Wong-Staal et al* (US 2001/0007659) is withdrawn in view of claim amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Previous rejections under this section have been modified in view of claim amendment.

Claims 1, 3-6, 8, 10, 12, 13, 31, 33, 34, 37-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Sedlacek et al* (US 6,358,524), in view of *Wong-Staal et al* (US 2001/0007659), and *Paul et al* (US 5,736,387).

Sedlacek et al teach a method for inserting genes into cells comprising delivering a complex into cells of an organism (abstract). The complex comprises,

a). a non-viral carrier such as liposome, proteins (column 2, lines 60-65), and cationic amphiphile/DNA complex (column 5, lines 26-67 and column 21, lines 54-64);

b). a ligand that binds specifically to the desired target cell such as membrane receptors on the surface of immune cells (column 9, lines 9-16);

c). a fusion protein for the penetration of the vector into the cytoplasm of the target cell, such as fusogeneic protein gp41 (column 17, lines 14-19); and

d). a gene to be introduced in the form of nucleic acid containing the corresponding gene (immunogenic or non-immunogenic) provided with regulatory regions, preferably as a plasmid (column 5, lines 20-25).

Sedlacek et al do not specifically teach the CD28 receptor ligand or fusing the gp41 as part of the ligand.

Wong-Staal et al teach a method of introducing a nucleic acid molecule carried by a lentiviral vector into a dendritic cell that expresses CD80 and/or CD86 (page 4, paragraph 0031) comprising incorporating a binding domain for CD86 such as CD28 (containing the extracellular region) in the coat protein of the retrovirus comprising the lentiviral vector, and administering such to a cell (examples 4 & 6) or a subject (example 7). They teach that the lentiviral vector of the invention is capable of transferring a nucleic acid preferably DNA into a dendritic cell (paragraph 0038). *Wong-Staal et al* do not teach using a cationic amphiphile/DNA complex or a fusion ligand for nucleic acid delivery.

Paul et al teach a chimeric (fusion) targeting ligand for directing gene delivery vehicle to specific mammalian cells, wherein the ligand comprises a ligand moiety

capable of binding to receptors present on target cells, and an uptake moiety capable of promoting entry of the vector into the target cell (abstract), wherein the ligand moiety could be any cytokine and analog (column 10, line 34-39), wherein the uptake moiety could be the gp41 of HIV virus including the cytoplasmic and transmembrane regions (column 16, particularly line 52). *Paul et al* do not specifically teach the CD28 ligand.

However, it is known in the art that a nucleic acid such as a DNA plasmid could be delivered to a cell with the aid of a cationic amphiphile/DNA complex, a targeting ligand, and a protein gp41 that promotes cellular uptaking as taught by *Sedlacek et al*, it is also known in the art that the ligand could be a fusion protein comprising portions with different functions of targeting and cellular uptaking (gp41) as taught by *Paul et al*; it is also well known that the targeting ligand could be a CD28 when the target cell is a dendritic cell as taught by *Wong-Stall et al.* Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Sedlacek et al, Wong-Stall et al and Paul et al*, by simply selecting CD28 and gp 41 as the ligand fusion partners with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because CD28 should target the nucleic acid specifically to dendritic cells, and the gp41 uptake moiety in the chimeric targeting protein provides additional means for delivering nucleic acids into the cells. Given the numerous choice of receptors and fusogens known in the art, it is a matter of optimization and customization for the reasonably skilled to select a combination of targeting and uptaking moiety for the target cells of

interest. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In the 1/27/04 response, applicants argue that the compositions taught in *Sedlacek et al* are distinct and function differently compared to those of *Wong-Stall et al and Paul et al* (non-viral vector vs. viral vector), and neither *Wong-Stall et al* nor *Paul et al*, teaches or suggests using non-viral particles as a delivery vehicle nor using the ligand or gp41 in a non-viral vector. Applicants go on to argue that Paul et al do not specifically teach or suggest a chimeric targeting ligand that can comprise CD28 or a portion. One skilled in the art would not consider combining the teachings of RNA with DNA delivery.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the rejection as modified, *Sedlacek et al* reference is relied upon as a showing of using a non-cellular particle combined with a ligand to deliver a DNA nucleic acid, the *Paul et al* reference is relied upon as a showing of using a fusion protein as the ligand, wherein the ligand comprises a portion that targets a cell receptor, and another portion (preferably gp41) that increases cellular uptake of a nucleic acid, and the *Wong-Stall et al* reference is relied on as a showing of using CD28 to target a surface receptor of dendric cells that express CD80/CD86. Apparently, the combined references have shown that it is known in the art that the ligand and the gp41 could be

used in delivering both DNA (*Sedlacek et al*) and RNA (*Paul et al* and *Wong-Stall et al*). In response to applicant's argument that there is no motivation to combine, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Here, the combined teachings would have reasonably suggested to those of ordinary skill in the art to select CD28 and gp41 as the ligand fusion partners for delivery a DNA nucleic acid to dendritic cells.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist **Rena Jones** whose telephone number is **571-272-0571**.

Q. Janice Li
Patent Examiner
Art Unit 1632

JANICE LI
PATENT EXAMINER

QJL
March 29, 2004